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Supplementary Text 1: ECG DEFINITIONS

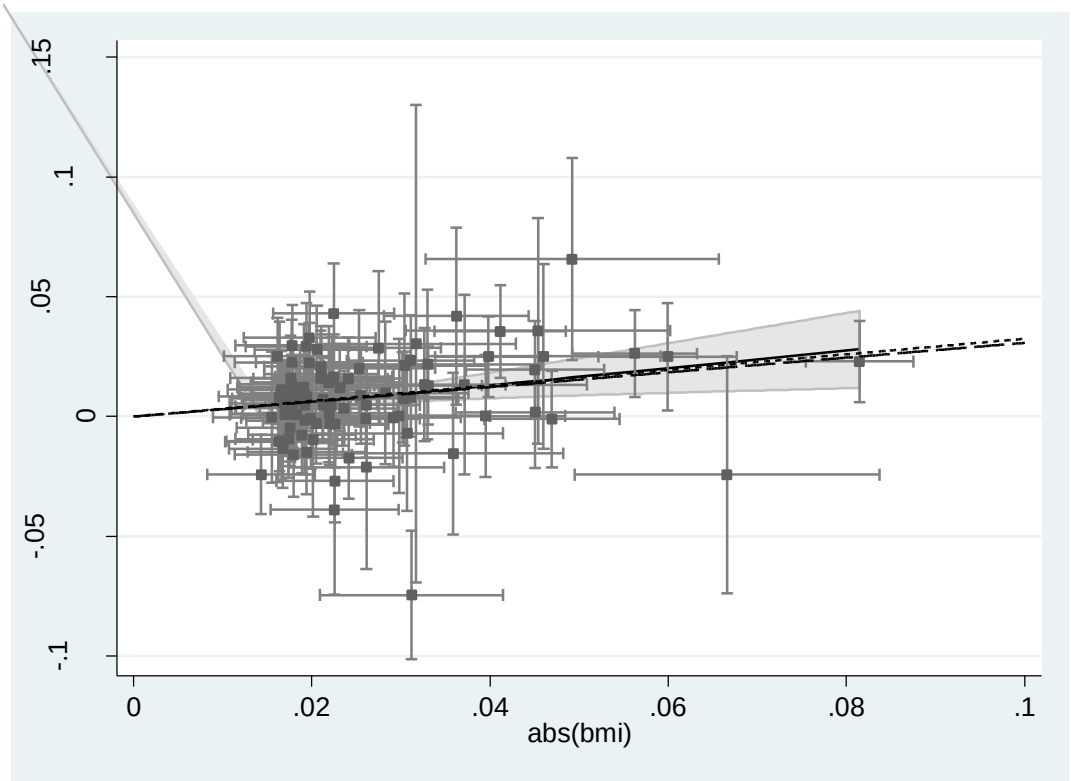
Definitions of the 12-lead ECG-LVH Indices Analyzed

- Sokolow-Lyon index (μV)=SV1+max (RV5, RV6)[3]
- Cornell product (μV · s)=Cornell voltage×QRS Duration (where Cornell voltage=RaVL+SV3 (600 μV added for females)[4]
- QRS voltage sum (μV)=the sum of |Q| +R+|S|+R'+|S|' amplitudes in all 12 leads[5,6]
- QRS voltage product (μV · s)=QRS voltage sum×QRS duration[5,6]

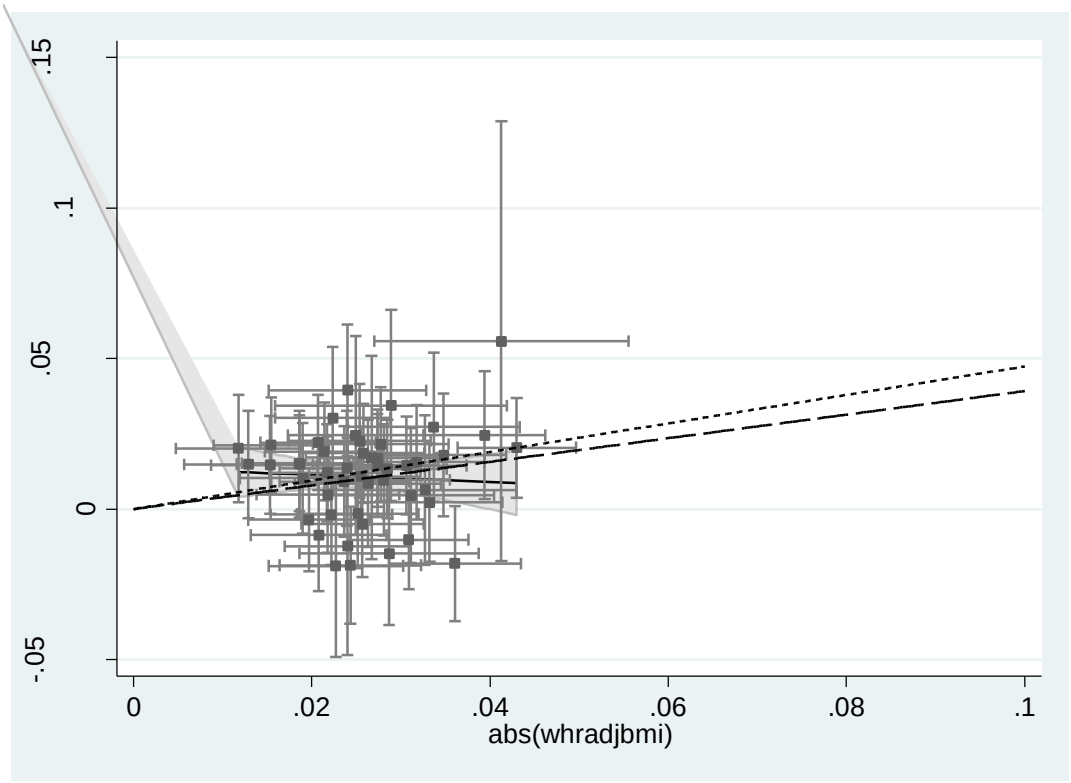
Reference: Shah S, Nelson CP, Gaunt TR, van der Harst P, Barnes T, Braund PS, Lawlor DA, Casas JP, Padmanabhan S, Drenos F, Kivimaki M, Talmud PJ, Humphries SE, Whittaker J, Morris RW, Whincup PH, Dominiczak A, Munroe PB, Johnson T, Goodall AH, Cambien F, Diemert P, Hengstenberg C, Ouwehand WH, Felix JF, Glazer NL, Tomaszewski M, Burton PR, Tobin MD, van Veldhuisen DJ, de Boer RA, Navis G, van Gilst WH, Mayosi BM, Thompson JR, Kumari M, MacFarlane PW, Day IN, Hingorani AD, Samani NJ.; Four Genetic Loci Influencing Electrocardiographic Indices of Left Ventricular Hypertrophy; Circulation: Cardiovascular Genetics 2011; 4:626-635

Supplementary Figures 1a-g: Scatter plots of MR-Egger model adding IVW line (long dash) and weighted median (short dash) for comparison

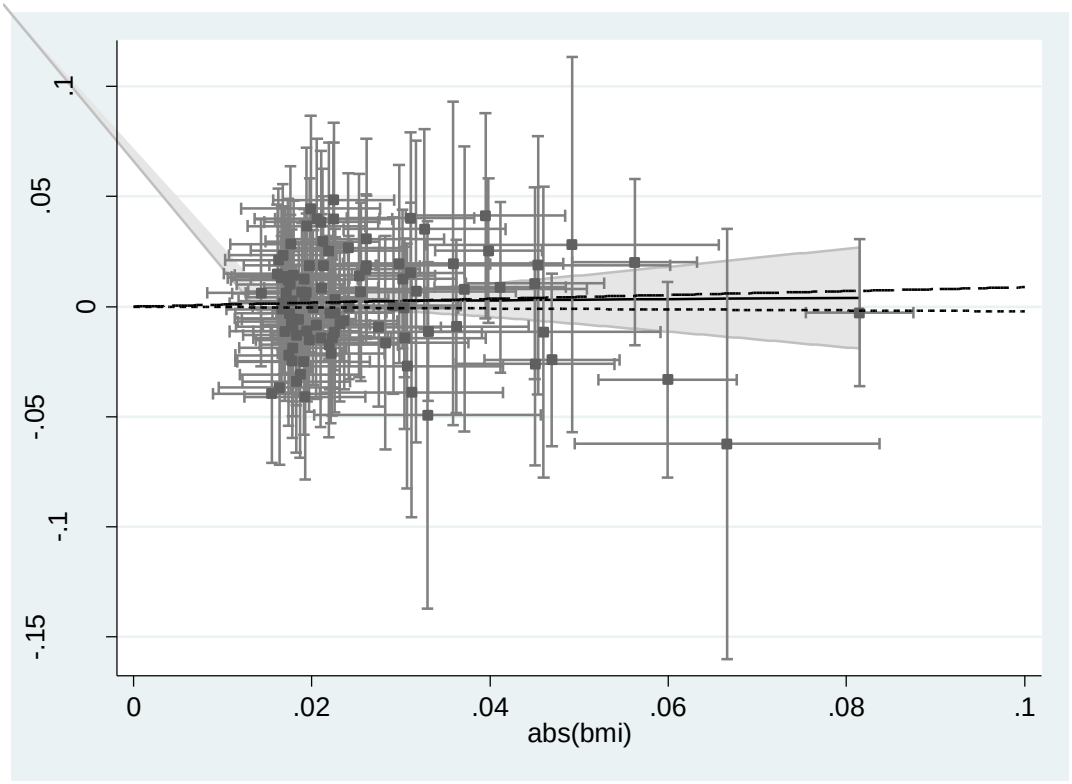
1a) BMI SNPs and CHD



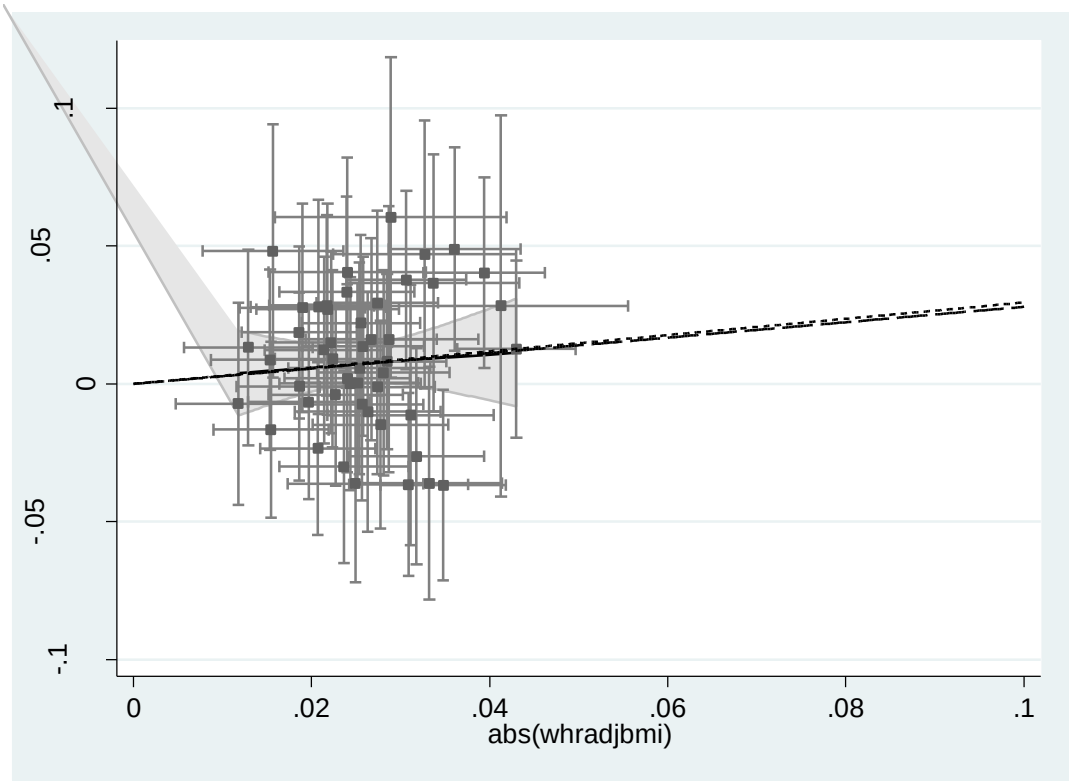
1b) WHRadjBMI SNPs and CHD



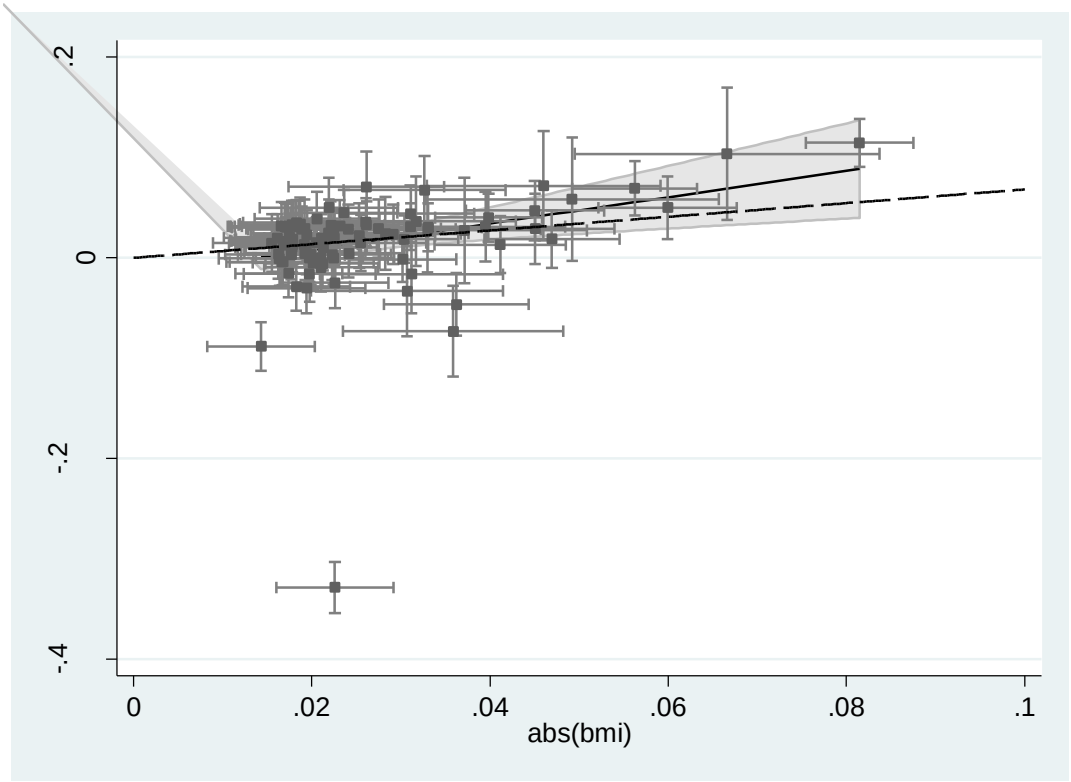
1c) BMI SNPs and ischaemic stroke



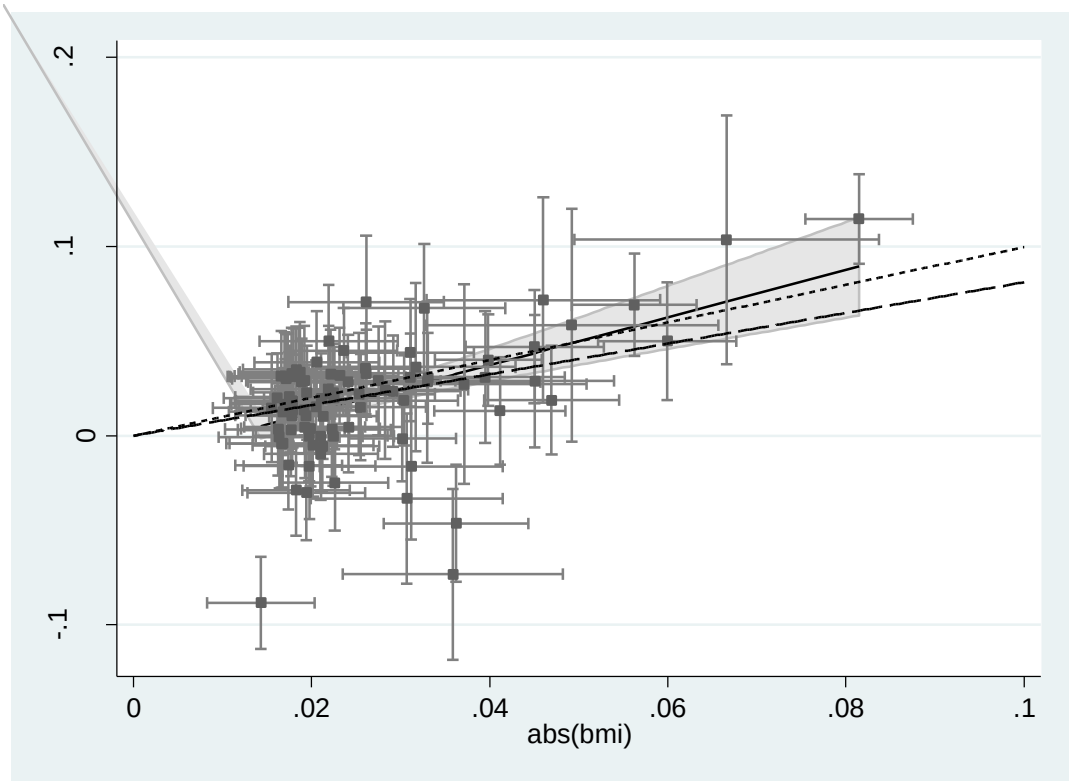
1d) WHRadjBMI SNPs and ischaemic stroke



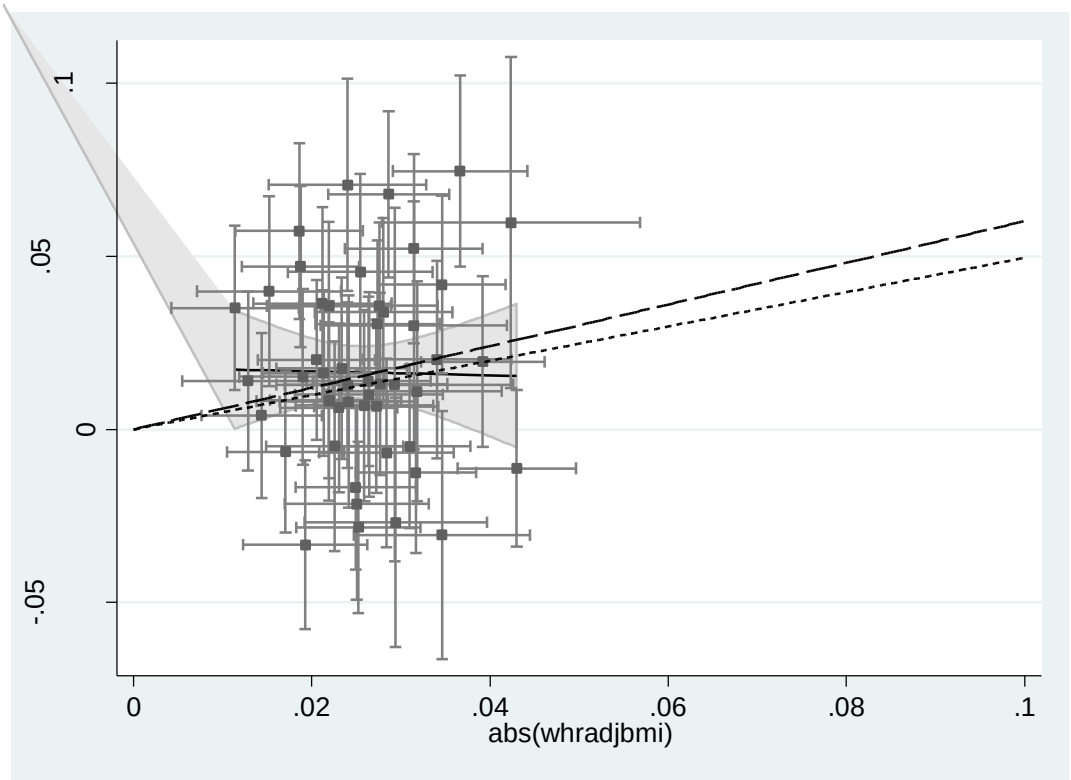
1e) BMI SNPs and T2D



1f) BMI snps (minus rs7903146) and T2D



1g) WHRadjBMI SNPs and T2D

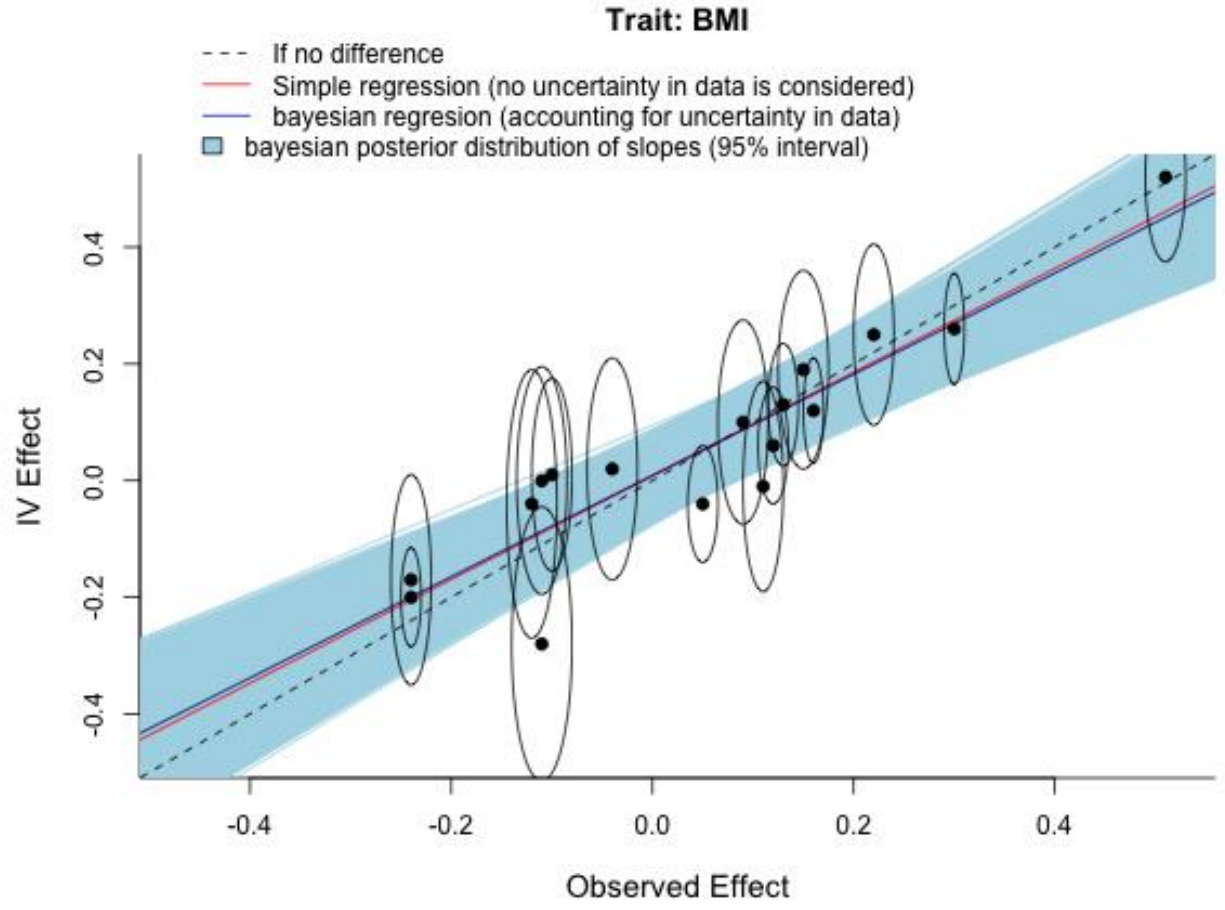


Supplementary Text 2: Comparison of IV and observational estimates in IPD

We compared the observational estimates to the IV estimates for all cardiometabolic traits (except anthropometric) to investigate similarity between the two methodological approaches for calculating an effect. A consistently higher or lower IV estimate could help to illuminate the direction of confounding in observational estimates, under the hypothesis that the IV estimate is calculated with less bias from conventional sources. Similarity between the observational and IV approaches may indicate estimation of the true causal effect by both methods, although a consistent effect of bias(es) in both methods cannot be ruled out.

We fitted a simple regression line of the instrumental variable estimated effects against the observational estimated effects of the cardiometabolic traits and compared this to the scenario of the two methods producing exactly the estimate (indicated by the black dotted diagonal line on the figures with slope equal to 1). In addition, we fitted a Bayesian regression model that takes into account the uncertainty associated with each of these two estimates. Each point estimate was assumed to arise from a normal distribution centred on the unknown true effect (instrumental variable or observational) with standard deviation equal to their estimated standard errors. The model was calculated using MCMC with a Gibbs sampling algorithm implemented in the software JAGS and we shaded a blue area covering the posterior 95% belief for the true regression line. These analyses were conducted in R.

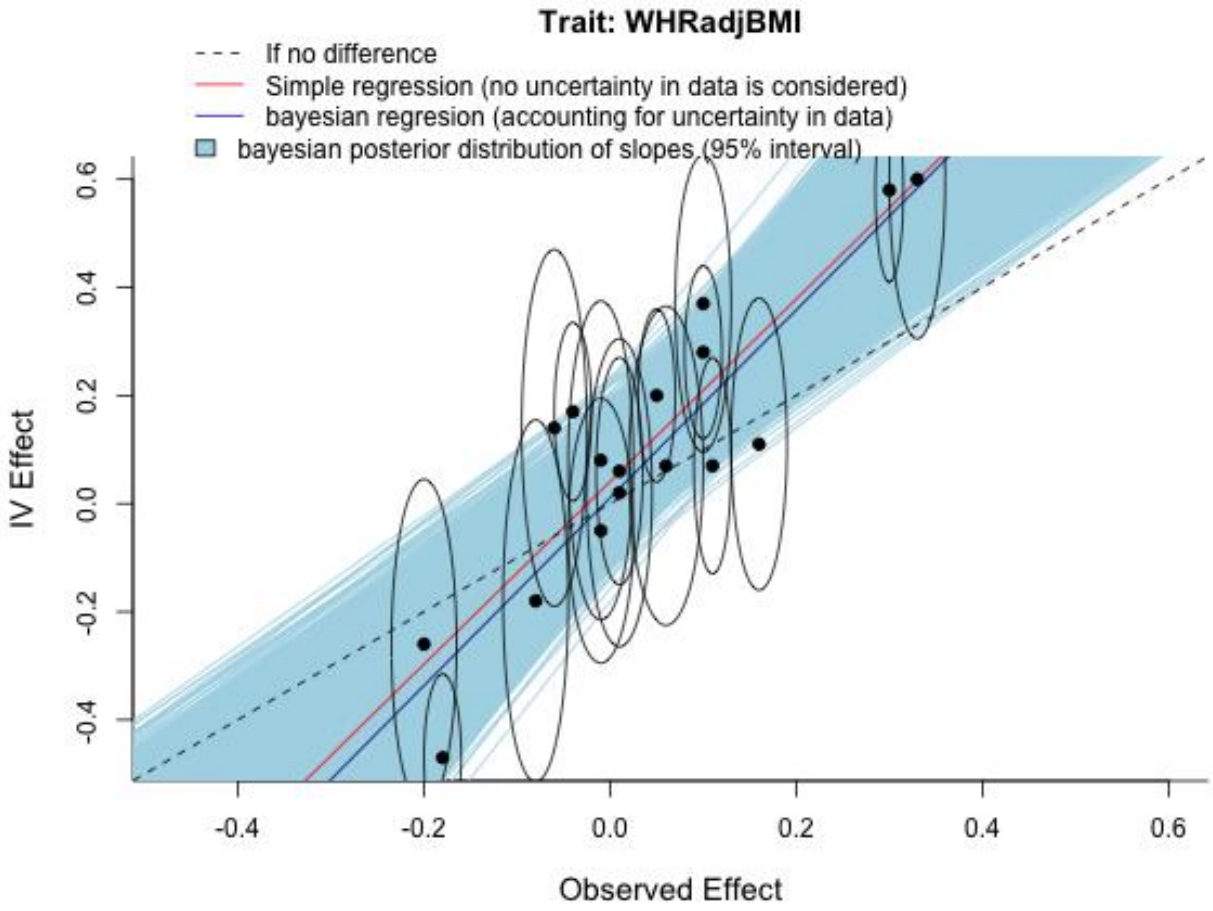
Supplementary Figure 2a: Comparison of association between BMI and cardiovascular traits derived from observational and MR estimates



Footnote: Each point represents SD change in CVD trait per 1SD increase in BMI

Overall, the linear relationship between observational and IV estimates across cardiometabolic traits, indicates that very similar estimates were produced by both methods for BMI. The difference between regression lines plotted with Bayesian regression (which accounts for uncertainty in the data) and without uncertainty was very small with the blue and red lines lying very close to each other. Furthermore, the black dotted line (indicating no difference) falls within the shaded blue area of the 95% posterior belief of the Bayesian regression slope.

Supplementary Figure 2b: Comparison of association between WHRadjBMI and cardiovascular traits derived from observational and MR estimates



Footnote: Each point represents SD change in CVD trait per 1SD increase in WHRadjBMI

For WHRadjBMI, we observe a greater difference between the observational and IV estimates, particularly for cardiometabolic traits where effects are larger. However, the black dotted line remains mostly within the blue shaded area indicating that the data are consistent with no true difference between methodological approaches.